2. *Support for the Amendments*

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally filed. No new matter is introduced by this Amendment.

3. *Rejections Under 35 U.S.C. § 112, second paragraph*

Claims 4, 6-8, 11, 14-16, 18-20, 22-24, 28, 30, 32-37 and 61-67 were rejected as indefinite under 35 U.S.C. 112, second paragraph. The claims as amended are fully supported by the specification as filed and in compliance with the statute, as described below. It is respectfully requested that this rejection be withdrawn.

A. Recitation of a final process step that relates back to the preamble

Claims 4, 6-8, 11, 14-16, 18-20, 22-24, 28, 30, 32-37 and 61-67 were rejected for allegedly failing to recite a final process step that clearly relates back to the claim preamble. The Examiner requested clarification as to "whether the claims are intended to require detection of a nucleic acid or 'obtaining' a nucleic acid. Claim 4 has been amended to recite a step (d) of recovering the recombinant herbicide tolerance nucleic acid.

B. Claims 65 and 66

Claims 65 and 66 were rejected as allegedly unclear with regard to whether steps (a) and (b) of claim 65 "are intended to further limit previously recited steps (a) and (b), respectively, or whether the method further comprises and an additional step (a) and an additional step (b)." The instant amendment makes clear that claim 65 is intended to further limit the previously recited steps (a) and (b).

4. *Rejections Under 35 U.S.C. § 103*

Claims 4, 6-7, 11, 14-16, 18-20, 23-24, 28, 30, 32-33, 35-37 and 61-67 have been rejected under 35 U.S.C. 103 as being unpatentable over Khosla et al. in view of Subramanian et al. and Sack et al.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. With respect to the instant claims these criteria have not been met, and withdrawal of the rejection is respectfully requested.

Claim 4 (and by reference to claim 4 all of the pending claims) has been amended to recite a step (c) of screening a library of recombinant nucleic acids for one that encodes an herbicide tolerance polypeptide that catalyzes the conversion of phosphoenolpyruvate plus shikimate-3-phosphate to 5-enolpyruvylshikimate-3-phosphate, i.e., the reaction catalyzed by EPSP synthase ("EPSPS"). The library is produced by recombining a plurality of nucleic acid segments derived from variant forms of a gene that encodes UDP-N-acetylglucosamine enolpyruvyltransferase (referred to hereafter as "EPT").

The Examiner asserts that it would have been obvious to apply the method of Khosla to variant forms of EPT and to screen the resulting recombinant libraries for herbicide tolerance, including glyphosate tolerance and novel mechanisms of glyphosate tolerance. However, the cited references do not suggest or motivate one to screen a library of EPT variants for an herbicide tolerance polypeptide that catalyzes the reaction normally catalyzed by EPSPS.

Sack describes EPT as a bacterial enzyme of potential pharmaceutical interest as a target for antibiotics, noting a certain degree of sequence similarity between EPT and EPSPS, but goes on to point out that "their reaction mechanisms appear to be substantially different". Sack states that the reaction pathway of EPT appears to involve the formation of a covalent intermediate, while the EPSPS reaction proceeds through a noncovalently bound tetrahedral intermediate. Sack also notes that EPSPS is not inactivated by fosfomycin (an inhibitor of EPT), and that glyphostate (an inhibitor of EPSPS) exerts no effect of EPT, further supporting the idea that the mechanisms of the two enzymes differ substantially.

Khosla describes a method based on generalized recombination for generating multiple protein variants. The method involves recombining sets of allelic mutants. Importantly, there is nothing in Khosla or elsewhere on the record that would suggest or motivate one to apply the method of Khosla in a manner whereby one enzyme is used as the starting material for the production of a different, novel enzyme capable of catalyzing a different reaction. In the case of the instant invention we are talking about a reaction that normally proceeds by a completely different mechanism and involves a substantially different substrate and product.

Furthermore, the cited references do not provide any suggestion or motivation to change the enzymatic mechanism of EPT to convert it into an EPSPS. In fact, the cited references do not suggest the desirability or feasibility of converting any enzyme that does not naturally catalyze the EPSPS reaction into one that does. Nothing on the record would suggest that EPT is of any practical interest other than as an antibiotic target, or that EPT or any derivative of EPT could be usefully expressed in a plant. The combination of the references

appears to be based on hindsight reconstruction, which the courts and MPEP have found to be improper. See, e.g., MPEP 2145.X.A.

Claim 65 depends upon claim 4 and recites the additional limitation of recombining an EPSPS nucleic acid segment with the plurality of EPT nucleic acid segments. The teaching of Khosla is limited to recombination of **allelic mutants**. In fact, the Khosla method relies on homologous recombination between closely related sequences, and generally would not be expected to be effective with sequences that are not allelic mutants of one another. EPSPS and EPT are clearly not allelic mutants of one another. For this reason, as well as the other reasons discussed above, it is respectfully submitted that a prima facie case of obviousness has not been established for claim 65, or for its dependent claim 66.

Withdrawal of this rejection is respectfully requested.

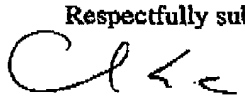
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-298-5884.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0990.

Respectfully submitted,



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Marked Copy Of Amended Claims for

USSN 09/373,333

4. (thrice amended) A method of obtaining a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide, wherein expression of the herbicide tolerance polypeptide at effective levels in a cell renders the cell tolerant towards an herbicide, the method comprising:

(a) providing a plurality of nucleic acid segments derived from a plurality of variant forms of a gene, wherein the gene encodes a UDP-N-acetylglucosamine enolpyruvyltransferase;

(b) recombining the plurality of nucleic acid segments to produce a library of recombinant nucleic acids; [and]

(c) screening the library to detect a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide that catalyzes the conversion of phosphoenolpyruvate plus shikimate-3-phosphate to 5-enolpyruvylshikimate-3-phosphate, wherein expression of the herbicide tolerance polypeptide at effective levels in the cell renders the cell tolerant towards the herbicide; and

(d) recovering the recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide having EPSP synthase activity.

65. (amended) The method of claim 4, wherein [the method further comprises]:

[(a)] step (a) further comprises providing an EPSP synthase nucleic acid segment derived from a gene that encodes an EPSP synthase; and

[(b)] step (b) further comprises recombining the EPSP synthase nucleic acid segment with the plurality of nucleic acid segments to produce the library of recombinant nucleic acids.

Courtesy Copy Of Pending Claims For

USSN 09/373,333 As Amended

4. (thrice amended) A method of obtaining a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide, wherein expression of the herbicide tolerance polypeptide at effective levels in a cell renders the cell tolerant towards an herbicide, the method comprising:

(a) providing a plurality of nucleic acid segments derived from a plurality of variant forms of a gene, wherein the gene encodes a UDP-N-acetylglucosamine enolpyruvyltransferase;

(b) recombining the plurality of nucleic acid segments to produce a library of recombinant nucleic acids;

(c) screening the library to detect a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide that catalyzes the conversion of phosphoenolpyruvate plus shikimate-3-phosphate to 5-enolpyruvylshikimate-3-phosphate, wherein expression of the herbicide tolerance polypeptide at effective levels in the cell renders the cell tolerant towards the herbicide; and

(d) recovering the recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide having EPSP synthase activity.

6. (twice amended) The method of claim 4, wherein the plurality of variant forms comprises allelic or interspecific variants of the gene.

7. (twice amended) The method of claim 4, wherein the plurality of variant forms is produced by synthesizing a plurality of nucleic acids homologous to the gene.

8. (twice amended) The method of claim 4, wherein the plurality of variant forms is produced by error-prone transcription of the gene or by replication of the gene in a mutator cell strain.

11. (amended) The method of claim 4, wherein the herbicide is glyphosate.

14. (twice amended) The method of claim 4, wherein the library of recombinant nucleic acids is present in a population of cells.

15. (as filed) The method of claim 14, wherein the screening comprises growing the population of cells in or on a medium comprising the herbicide and detecting a physical difference between the herbicide and a modified form of the herbicide produced by the cells.

16. (as filed) The method of claim 15, wherein the physical difference between the herbicide and the modified form of the herbicide is detected by a difference in fluorescence or absorbance between the herbicide and the modified form of the herbicide.

18. (as filed) The method of claim 14, wherein the screening comprises growing the population of cells in or on a medium comprising the herbicide and selecting for enhanced growth of the cells in the presence of the herbicide.

19. (amended) The method of claim 18, wherein enhanced growth of the cell requires the expression of the herbicide tolerance polypeptide at effective levels in the cell.

20. (amended) The method of claim 19, wherein enhanced growth of the cell requires a product of a reaction catalyzed by the herbicide tolerance polypeptide.

22. (amended) The method of claim 19, wherein the cells are an AroA$^-$ strain of bacteria, the herbicide is glyphosate, and the recombinant herbicide tolerance nucleic acid encodes a polypeptide that catalyzes the conversion of phosphoenolpyruvate plus shikimate-3-phosphate to 5-enolpyruvylshikimate-3-phosphate.

23. (twice amended) The method of claim 4, the method further comprising screening the library for an additional activity that confers tolerance to an additional herbicide.

24. (twice amended) The method of claim 4, wherein the recombining is performed in a population of cells.

28. (twice amended) The method of claim 4, wherein the method further comprises:

(d) recombining a recombinant herbicide tolerance nucleic acid detected in step (c) with an additional nucleic acid, wherein the additional nucleic acid is the same or different from the plurality of variant forms of a gene of step (a), to produce an additional library of recombinant nucleic acids; and

(e) screening the additional library to detect a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide, wherein expression of the herbicide tolerance polypeptide at effective levels in the cell renders the cell tolerant towards the herbicide; and, optionally

repeating steps (d) and (e).

30. (twice amended) The method of claim 4, wherein the library of recombinant nucleic acids is present in bacterial cells and the screening step comprises:

pooling a plurality of cells each comprising a separate member of the library produced in step (b);

screening the resulting pooled cells to detect a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide, wherein expression of the herbicide tolerance polypeptide at effective levels in the cell renders the cell tolerant towards the herbicide; and

isolating the recombinant herbicide tolerance nucleic acid.

32. (twice amended) The method of claim 4, further comprising transducing the recombinant herbicide tolerance nucleic acid into a plant.

33. (twice amended) The method of claim 4, further comprising transducing the recombinant herbicide tolerance nucleic acid into a plant and testing the resulting transduced plant for tolerance to an herbicide.

34. (twice amended) The method of claim 4, further comprising transducing the recombinant herbicide tolerance nucleic acid into a plant and breeding the plant with another plant strain of the same species, and selecting resultant offspring for tolerance to an herbicide.

35. (twice amended) A library of recombinant nucleic acids made by the method of claim 4.

36. (as filed) The library of claim 35, wherein the library is a phage display library.

37. (twice amended) A recombinant herbicide tolerance nucleic acid made by the method of claim 4.

61. (amended) The method of claim 4, further comprising isolating or recovering the recombinant herbicide tolerance nucleic acid.

62. (as filed The method of claim 4, wherein the gene is a *MurA* gene.

63. (as filed) The method of claim 62, wherein the gene is a bacterial *MurA* gene.

64. (as filed) The method of claim 63, wherein the bacterial *MurA* gene is selected from the group consisting of the genes corresponding to GenBank Accession Numbers M76452, Z11835, AF142781 and X96711.

65. (amended) The method of claim 4, wherein:

step (a) further comprises providing an EPSP synthase nucleic acid segment derived from a gene that encodes an EPSP synthase; and

step (b) further comprises recombining the EPSP synthase nucleic acid segment with the plurality of nucleic acid segments to produce the library of recombinant nucleic acids.

66. (as filed) The method of claim 65, wherein the EPSP synthase nucleic acid segment is derived from the S3P binding region of an EPSP synthase gene.

67. (as filed) The method of claim 28, wherein the additional nucleic acid is derived from a gene that encodes an EPSP synthase.